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Short Note

Ethyl 5-(4-Bromophenyl)-4-methyl-1*H*-pyrrole-2-carboxylate

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Abstract: This note describes a sequence converting an oxime-substituted pyrrolidine into a trisubstituted pyrrole structure. The synthetic route is based on a double chlorination of the pyrrolidine substrate followed by the base induced formation of both an imine and a nitrile oxide functionality. The latter reacts with an immobilized thiourea to yield an isothiocyanate which upon elimination generates the final pyrrole in an unprecedented cascade of events.

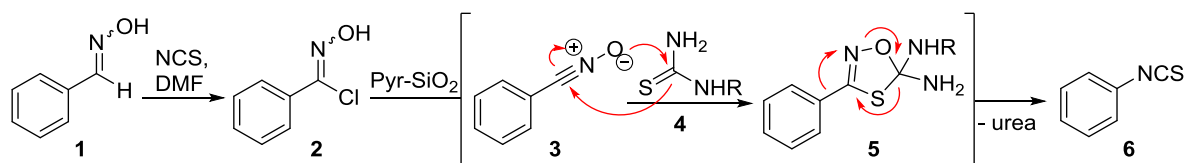
Keywords: pyrrole; pyrrolidine; heterocycle; rearrangement; isothiocyanate; chlorination

1. Introduction

Pyrroles are amongst the most prevalent electron-rich heteroaromatic architectures and can be found in the structures of numerous materials, drugs, and natural products [1–3]. Consequently, many synthetic routes are described for their assembly [4]. Most commonly, these heterocycles arise from acyclic precursors via cyclocondensation or cycloaddition approaches. It is therefore desirable to develop new routes towards highly substituted pyrroles that harness alternative synthetic strategies, especially if these explore unprecedented transformations or reaction cascades [5].

2. Results

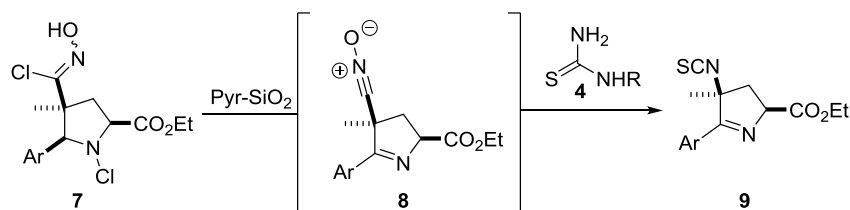
In a recent research project [6], we reported on a flow-based transformation of chloro-oximes (2) to isothiocyanates (6) via the intermediacy of a nitrile oxide dipole (3) that underwent a [3 + 2]-cycloaddition with a thiourea species (4). As indicated in Scheme 1, a skeletal rearrangement of the initial cycloadduct 5 subsequently rendered the desired isothiocyanate product 6.



Scheme 1. Previous synthesis of isothiocyanates via a dipolar cycloaddition approach.

During this study, we also subjected some more elaborate substrates, such as substituted pyrrolidines [7], to this sequence and were pleased to obtain the expected isothiocyanate. However, we also observed the simultaneous generation of a cyclic imine functionality, which indicated that chlorination had not only occurred on the oxime to yield a chloro-oxime, but also on the pyrrolidine nitrogen (7, Scheme 2). Upon treatment of this dichlorinated material (7) with silica-supported pyridine (Pyr-SiO₂, 2.5 equiv.) both the highly reactive nitrile oxide and the more stable oxime were generated, subsequently leading to the corresponding isothiocyanate product 9. Importantly, this

procedure worked equally well for diastereopure samples, as well as mixtures of diastereomers at the quaternary carbon.



Scheme 2. Concomitant imine formation for pyrrolidine substrates.

In a more recent extension to this work, we investigated an increase in the stoichiometric excess of base which unexpectedly led to a different product outcome. When a solution of **7** (Ar = 4-bromophenyl, 2:1 mixture of diastereomers) was heated at 60 °C for 6 h in the presence of 3.5 equivalents of base complete conversion to the new species was observed. The new product was isolated and ¹H-NMR analysis revealed the disappearance of the diagnostic diastereotopic methylene protons, whilst a new resonance appeared at 6.8 ppm. Furthermore, a broad singlet was found at 9.0 ppm that was assigned as a NH proton. Interestingly, subjecting product **9** instead of **7** (Ar = 4-bromophenyl) to the analogous reaction with 1.5 equivalents of base (either Pyr-SiO₂ or NEt₃) gave rise to the same product as the sole isolated species. Upon purification and recrystallization of this product, material crystals suitable for single crystal X-ray diffraction experiments were obtained. The crystal structure revealed that the pyrrolidine ring had undergone aromatization to the related pyrrole heterocycle (Figure 1). The X-ray shows that the pyrrole ring is twisted out of plane with respect to the arene ring by 27° due to the steric hindrance of the methyl group.

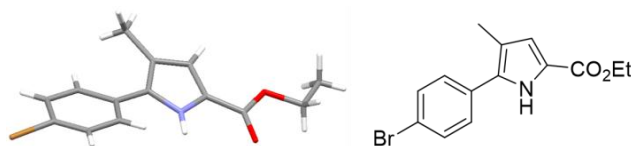
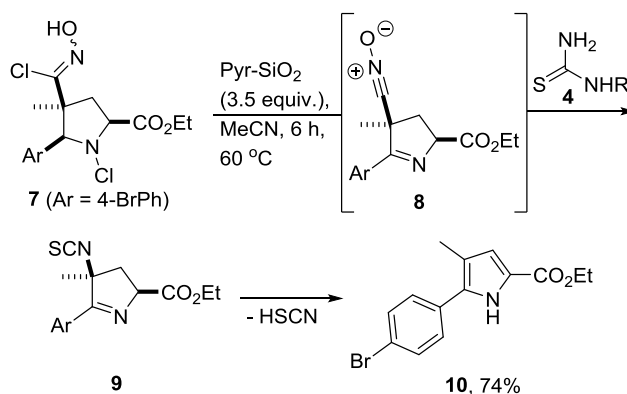


Figure 1. Crystal structure of pyrrole **10** (CCDC 1562557) [8].

3. Discussion

To account for this process, we propose a mechanism consistent with the above-mentioned formation of imine intermediate **9**, which thus requires 2 equivalents of base to remove the HCl formed. A further equivalent of base is then required to eliminate thiocyanic acid (HSCN) to furnish pyrrole product **10** (Scheme 3).



Scheme 3. Proposed mechanism for the formation of pyrrole **10**.

4. Materials and Methods

A solution of the dichloride **7** (Ar = 4-BrPh) was freshly prepared by adding *N*-chlorosuccinimide (NCS, 1.1 mmol, 147 mg, 2.2 equiv.) to a solution of the corresponding oxime (1.0 mmol, 175 mg, d.r. 2:1) in DMF (2 mL). After stirring this mixture for 4 h at ambient temperature, diethyl ether (10 mL) and water (10 mL) were added and the mixture was extracted into diethyl ether. The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated to dryness to yield the crude dichloride intermediate as a colorless oil. This material was redissolved in MeCN (6 mL) and combined with silica-supported pyridine (2.45 g, 3.5 equiv., [9]) and an immobilized thiourea (QP-SA, 500 mg, 2.0 mmol, 4.0 equiv., [10]). After heating the resulting mixture at 60 °C for 6 h, complete conversion of substrate was observed by TLC. Filtration and evaporation yielded a yellow oil that was further purified by silica column chromatography (10–20% EtOAc/hexanes) to furnish pyrrole **10** as a colorless solid, which was recrystallized from DCM/toluene giving the desired product as colorless crystals (74%, 114 mg). Please see SI for further information.

¹H-NMR (600 MHz, CDCl₃) δ/ppm 9.03 (1H, br s, NH), 7.96 (2H, d, *J* = 8.0 Hz), 7.35 (2H, d, *J* = 8.0 Hz), 6.80 (1H, d, *J* = 2.6 Hz), 4.32 (2H, q, *J* = 7.2 Hz), 2.23 (3H, s), 1.35 (3H, t, *J* = 7.2 Hz). ¹³C-NMR (150 MHz, CDCl₃) δ/ppm 161.1 (C), 132.2 (C), 132.0 (2CH), 131.2 (C), 128.4 (2CH), 121.9 (C), 121.4 (C), 118.7 (C), 118.0 (CH), 60.4 (CH₂), 14.5 (CH₃), 12.4 (CH₃). IR (neat, cm^{−1}) ν 3305 (m), 2976 (w), 1685 (s), 1463 (m), 1281 (s), 1217 (s), 1184 (s), 1073 (m), 1032 (m), 1007 (m), 830 (m), 764 (m). HRMS (TOF MS AP+) calculated for C₁₄H₁₄⁷⁹BrNO₂ 307.0208, found 307.0191 (Δ 1.7 mDa). X-ray data: CCDC 1562557; space group P-1; *a* = 4.8001(3) Å, *b* = 11.6381(6) Å, *c* = 11.6810(6) Å; α = 86.908(2)°, β = 86.919(2)°, γ = 89.587(2)°.

5. Conclusions

In conclusion, we describe an efficient reaction sequence converting an oxime bearing pyrrolidine into its pyrrole counterpart. This is based on dichlorination of the oxime substrate followed by treatment with excess base and an immobilized thiourea species, triggering a series of events including formation of a cyclic imine, rearrangement of the oxime into an isothiocyanate, and its subsequent elimination to render the final pyrrole product after tautomerization. The identity and connectivity of this structure was unambiguously established by single crystal X-ray diffraction experiments.

Supplementary Materials: The following are available online at www.mdpi.com/1422-8599/2017/3/M951: Copies of NMR spectra of **10**.

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Author Contributions: M.B. conducted the research and both M.B. and I.R.B. wrote the manuscript.

Conflicts of Interest: The authors declare no conflict of interest. The founding sponsors had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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7. These pyrrolidines are conveniently prepared by dipolar cycloaddition reactions between azomethine ylides and methyl methacrylate, giving the endo-diastereomer in preference over the exo-diastereomer. See reference [5] for further details.
8. The X-ray structure of pyrrole 10 has been deposited with the Cambridge Crystallographic Data Centre as CCDC 1562557.
9. Silica-supported pyridine (Pyr-SiO₂, 40–63 µm, 1.39 mmol/g) is commercially available from Silicycle.
10. QuadraPure™ Thiourea resin (QP-SA, loading 4.0–5.5 mmol/g) is commercially available from Johnson-Matthey.



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